

critical for binding. This is illustrated by the 10^5 - 10^6 decrease in affinity on going from Ala-boroPro or Pro-boroPro to boroPro itself (Table 1).

5 The inhibition experiments presented in Table 1 were carried out on DP-IV isolated from pig kidneys. Pro-boroPro and Ala-boroPro inhibit DP-IV from human placenta equally well.

10 The Ala-boroPro and Pro-boroPro used in the experiments described above were racemic mixtures in which the boroPro moiety was present as both the D-form and L-form while Ala and Pro were both the L-isomer.

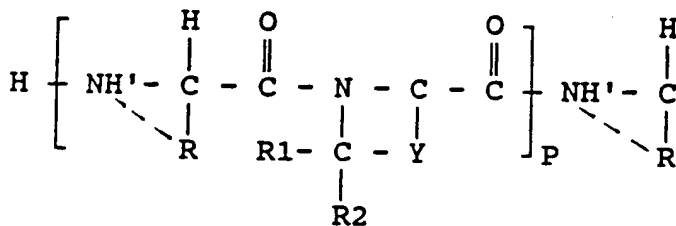
15 High pressure liquid chromatography (HPLC) can be used to separate L-Pro-D-boroPro from L-Pro-L-boroPro. A 4.6 mm x 250 mm Nucleosil C18 (5μ particle) column employing a two buffer system (Buffer A is 100% H_2O with 0.1% TFA, and buffer B is 70% CH_3CN , 30% H_2O , 0.86% TFA) can be used to carry out the separation. From 0 to 5 min 5% B and 95% A is used, and from 5 to 25 min 5% to 100% B is used. The L,L isomer comes off first at about 7 min, followed by the L,D isomer at about 10 min. NMR and mass spectra analysis were consistent with both compounds being Pro-boroPro. Rechromatography of the purified isomers indicated that the first pass on the HPLC column achieved an isomeric purity of about 99-6% for each isomer. High pressure liquid chromatography (HPLC) can similarly be used to be used to separate L-Ala-D-boroPro from L-Ala-L-boroPro or to separate the D-boroPro form of other inhibitors from the L-boroPro form.

25 30 When L-Pro-L-boroPro and L-Pro-D-boroPro were used in a DP-IV inhibition assay, the K_i for L-Pro-L-boroPro was $3.2 \times 10^{-11}M$, while for L-Pro-D-boroPro the K_i was $6.0 \times 10^{-8}M$. The L,L-isomer constitutes a much better

1. An inhibitor compound, having the structure

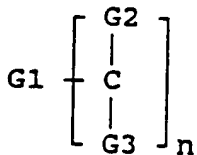
Group I - Group II

where Group I has the structure:



wherein each R, independently, is chosen from the group consisting of the R groups of an amino acid including proline; each broken line, independently, represents a bond to an H or a bond to one said R group, and each H' represents said bond or a hydrogen; p is an integer between 0 and 4 inclusive;

or Group I has the structure:



where n is between 0 and 3 inclusive,
each G2 and G3 independently is H or C1 - 3 alkyl,
G1 is NH3, NH - C - NH2, or



NG4, where G4 is C - G5

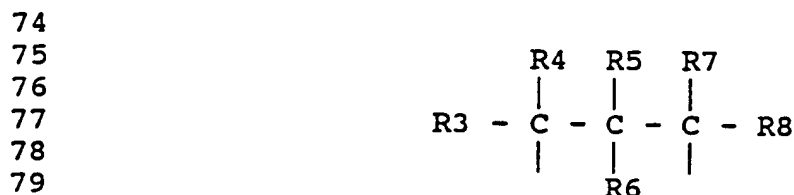
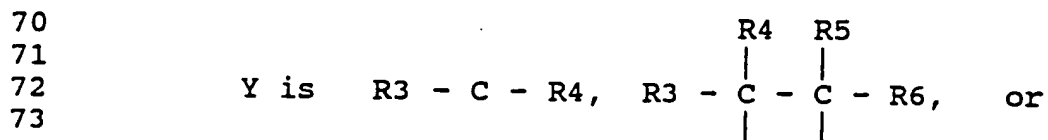


where G5 and G6 can be NH, H, or C1 - 3 alkyl or alkenyl with one or more carbons substituted with a nitrogen; provided that G1 bears a charge and G1 and Group II do not form a covalently bonded ring structure at pH 7.0;

or Group I has the structure:



where each J, independently, is O-alkyl, N-alkyl, or alkyl, each said O-alkyl, N-alkyl or alkyl comprising 1 - 20 carbon atoms and, optionally, heteroatoms which can be N, S, or O; said T being able to form a complex with the catalytic site of a dipeptidyl-aminopeptidase type IV (DP IV) enzyme;



and each R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈, separately is a group which does not significantly interfere with site specific recognition of said inhibitory compound by said DP IV, and allows said complex to be formed with said DP IV.

2. The compound of claim 1, wherein T is a boronate group.

3. The compound of claim 1, wherein T is a phosphonate group or a trifluoroalkyl ketone group.

4. The compound of claim 1 wherein each R₁ - R₈ is H.

1 5. The compound of claim 1 or 2 wherein each R1 and
2 R2 are H, and each Y is CH₂ - CH₂.

1 6. The compound of claim 5 wherein each R is
2 independently chosen from the R group of proline and
3 alanine.

1 7. The compound of claim 1, wherein said compound
2 has a binding or dissociation constant to said DP IV of at
3 least 10⁻⁹M.

1 8. The compound of claim 1, wherein said compound
2 has a binding constant to said DP IV of at least 10⁻⁸M.

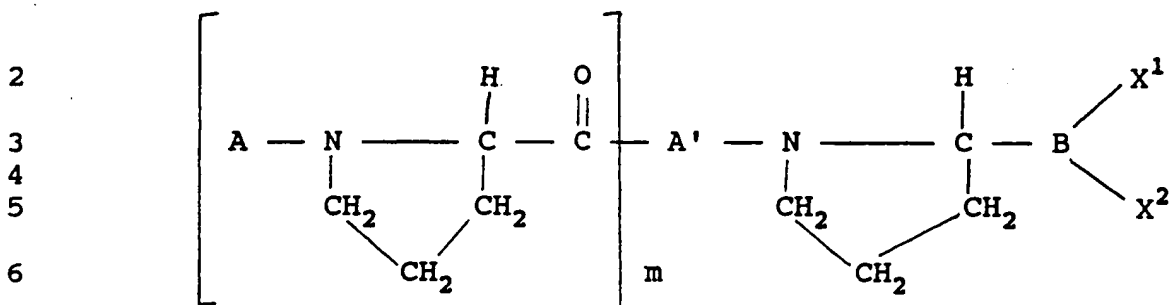
1 9. The compound of claim 1 admixed within a
2 pharmaceutically acceptable carrier substance.

1 10. The compound of claim 1 wherein, each D1 and D2
2 is, independently, F or D1 and D2 together are a ring
3 containing 1 to about 20 carbon atoms, and optionally
4 heteroatoms which can be N, S, or O.

1 11. A method for inhibiting DP IV in a mammal,
2 comprising administering to said mammal an effective amount
3 of a compound of claim 1.

1 12. The method of claim 11 wherein said amount is 1
2 - 500 mg/kg/day.

1 13. An inhibitor of DP-IV, having the structure:



7 wherein m is an integer between 0 and 10, inclusive; A and
8 A' are L-amino acid residues such that the A in each
9 repeating bracketed unit can be a different amino acid
10 residue; the C bonded to B is in the L-configuration; the
11 bonds between A and N, A and C, and between A and N are
12 peptide bonds; and each X¹ and X² is, independently, a
13 hydroxyl group or a group capable of being hydrolysed to a
14 hydroxyl group at physiological pH.

1 14. The inhibitor of claim 13 wherein A and A' are
2 independently proline or alanine residues.

1 15. The inhibitor of claim 13 wherein m is 0.

1 16. The inhibitor of claim 13 wherein X¹ and X² are
2 hydroxyl groups.

1 17. The inhibitor of claim 13 wherein said
2 inhibitor is L-Ala-L-boroPro.

1 18. The inhibitor of claim 13 wherein said
2 inhibitor is L-Pro-L-boroPro.

1 19. A method for inhibiting DP-IV in a mammal,
2 comprising administering to said mammal an effective amount
3 of a compound of claim 13.

1 20. The method of claim 19 wherein said amount is
2 1 mg/kg of said mammal per day to 500 mg/kg of said mammal
3 per day.